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PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Encapsulation of Particles by Liquid-liquid Phase Separation

We, THE UPJOHN COMPANY, a Corporation organised and existing under the Laws of the State of Delaware, United States of America, of 301, Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for the production of particles of material encapsulated within a membrane comprising polymeric material which has been formed around the particles by a liquid-liquid phase separation process, and in particular to a process which includes a step for hardening and increasing the impermeability of the membrane.

According to the invention, such a process includes the steps of: (1) forming the membranes about the particles of material by a liquid-liquid phase separation process; (2) setting the membranes; (3) hardening the membranes by irradiation thereof with beta rays, gamma rays or X-rays.

Membranes produced by this process exhibit marked improvements in hardness and impermeability over membranes produced by a similar process which does not include the irradiation step specified. The effect of the irradiation step is to chemically alter the structure of the membranes and this alteration cannot be reversed by physical means. Apart from the increase in impermeability and hardness of the membranes resulting from the irradiation, the encapulated particles are also sterilised by the irradiation.

The encapsulated particles produced by the process of this invention are valuable wherever a hard impermeable membrane is desired. Such a membrane is especially useful where either the encapsulated material has penetrating properties or the environment to which the encapsulated material is to be exposed has penetrating properties. For example, the encapsulated material can be employed in the printing art in the same manner as the products described in British Patent Specification No. 751,600, i.e., as a pressure-sensitive, reproducing film to replace carbon paper, especially where a highly penetrating material (e.g., a dye) is encapsulated or the finished product must withstand more rigorous handling and exposure conditions. It can be used to store otherwise incompatible mixtures where either the coated or uncoated material involved is a penetrating liquid. Oil products, such as vitamins or edible vegetable animal, or mineral fats and oils may also be encapsulated and are suitable for incorporation into dry cereals, margarine, ice cream, butter, milk and other dairy products, fruit and vegetable juices (e.g., orange juice), bread and other baked goods, jams and other condiments, and for maintaining unstable flavours, the mantle being broken in cooking or mixing.

The encapsulated material can thus include medicaments and dietary supplements which must be maintained in fluid form over long periods of time or in more penetrating fluids for relatively short periods of time. Orally ingestible materials which must resist immediate disintegration in certain environmental conditions existing in the gastrointestinal tract can also be encapsulated, and the membranes produced mask flavours or odours or result in sustained or controlled release of the encapsulated materials.

The term "liquid-liquid phase separation" as employed herein refers to the separation of a solution or a sol of polymer or combination of polymers into two distinct liquid phases, one designated as the polymer-rich phase and the other the polymer-poor phase. Where the polymer-rich and polymer-poor phases are colloidal sols rather than true solutions, the phenomenon of phase separation is herein designated as coacervation. Thus,

a coacervate is a polymer-rich sol which has separated from an original single-phase polymeric dispersion (either a solution or a sol), leaving behind a polymer-poor sol or equilibrium liquid. The separating phase appears initially as a fine dispersion of microscopic droplets of polymer in the equilibrium liquid. When formed in a pure colloidal system, these droplets are essentially homogeneously dispersed. However, if foreign materials are present in the original dispersion, the separating phase tends to form around these materials as membranes. Technically, the term coacervation relates to the process by which the liquid colloidal concentrate or coacervate is formed as a phase entity of the initial sol or solution. In its practical aspect, and as employed herein, coacervation relates to the process by which foreign materials present in the sol when the coacervate is formed are enveloped or encapsulated by the coacervate. Where the coacervate or separating phase consists of a single polymer, the process is termed simple coacervation or simple phase separation; where more than one polymer is present in the coacervate or separating phase the process is called complex coacervation or complex phase separation.

In order to obtain the maximum advantages of such a membrane as a means for enhancing the usefulness of a wide variety of materials, it is necessary that the membrane retains its integrity except under conditions where release of the encapsulated material is desired. This means that the membrane must have sufficient integrity to withstand normal usage in formulation and packaging. The membrane must also remain intact under all contemplated environmental conditions until an appropriate physical, chemical or mechanical agency of destruction is operative. In addition to resisting premature destruction, the membrane must be highly impermeable to the passage of molecules or ions which might adversely affect the encapsulated material. Alternatively, where slow release of materials enclosed within the membrane is desired, the coating structure must be of such permeability as to permit the gradual passage of environmental fluids to effect such release. Preparation of the membrane by the method of this invention yields a novel coating structure by which the foregoing properties can be obtained.

The particles of material which are encapsulated by the process of the invention may be solid particles having an external lipophilic surface or they may be particles of oil or particles composed of an oil-in-hydrophilic liquid emulsion in which the hydrophilic liquid contains a thickening agent, or they may be particles of a hydrophilic liquid-in-oil emulsion in which the oil contains an anti-inversion agent. The material of which the particles are composed may have dissolved or dispersed therein one or more active ingredients. By the term "active ingredient" we mean a substance which may be dispersed or dissolved in the material of which the particles to be encapsulated are composed but which will not substantially affect the process of liquid-liquid phase separation.

Various polymeric materials may be used to form the membrane in the process of the invention. Preferably, one or more gelable hydrophilic colloids are used as the polymeric material to form the membranes. Examples of suitable gelable hydrophilic colloid materials include gelatin, albumin, fibrinogen, casein, agar, sodium oleate, pectin, and ichthyocolla.

Other polymeric material may also be used either in place of or in addition to such gelable hydrophilic colloids. Such polymeric materials include linear macromolecular synthetic polymers, as hereinafter defined, gum acacia, sodium carboxymethylcellulose, sodium alginate, cellulose acetate phthalate, starch acetate phthalate, amylose acetate phthalate, and other polymeric materials which, like the preceding named materials, are opposite in charge to the gelable hydrophilic colloid, if such a gelable hydrophilic colloid is present. Coatings including gelable hydrophilic colloids are preferred in the process of the invention.

By the term "linear macromolecular synthetic polymer" we mean macromolecular polymers having an average molecular weight of at least 20,000 and having a linear, as opposed to a cross-linked, polymeric structure: for example, those whose polymeric structure comprises both lipophilic units and hydrophilic units, i.e., firstly, a recurring polymer unit which is essentially lipophilic in character and preferably comprises a single recurring group (e.g., one derived from styrene, an alkyl ring substituted styrene or an ether or ester substituted ethylene) but may also contain small amounts of other groups which may be either hydrophilic or lipophilic in character, the amount of any groups of hydrophilic character being such that the polymeric recurring unit retains its essentially lipophilic character, and secondly, a recurring polymer unit which is essentially hydrophilic in character and preferably comprises one recurring group (e.g., a group derived from maleic acid, maleic acid amide, acrylic acid, crotonic acid, acrylic acide amide) but may also contain small amounts of other groups of either hydrophilic or lipophilic character, the amounts of any groups of lipophilic character being such that the recurring unit retains its essentially hydrophilic character. Examples of the groups which may be present in small amounts in either recurring unit are groups derived from acrylonitrile, acrylic acid, methacrylic acid, itaconic acid, ethyl vinyl ether, methyl vinyl ether, vinyl

chloride, and vinylidene chloride. Examples of such macromolecular synthetic polymers are the hydrolysed styrene-maleic anhydride copolymers, styrene-maleic acid amide copolymers, sulphonated polystyrenes, polymethacrylic acid, and methyl vinyl ether-maleic acid copolymer. The preferred polymers of this class are the hydrolysed styrene maleic anhydride copolymers, the anhydride groups of which are preferably at least 50 per cent hydrolysed.

The preferred polymers of the above described type can be represented by the formula $-(-R-R^1-)-_n$ where R is a recurring unit which is comprised of groups of which at least 70 per cent are styrene residue so that R is essentially a lipophilic unit, the remaining groups comprising R being either hydrophilic or lipophilic in character, and R^1 is a recurring unit which is comprised of groups of which more than 50 per cent, and preferably more than 70 per cent, are maleic acid residues so that R^1 is essentially a hydrophilic unit, the remaining groups comprising R^1 being either hydrophilic or lipophilic in character, the said groups comprising R or R^1 which are of hydrophilic or lipophilic character being residues of ethylenic monomers such as those of acrylonitrile, acrylic acid, methacrylic acid, itaconic acid, vinyl chloride and vinylidene chloride, the ratio of $R:R^1$ being from 1:1 to about 4:1, preferably from 1:1 to about 1.2:1 and n is an integer from about 90 to 1,000. The average molecular weight of the copolymer preferably ranges from about 20,000 to about 200,000.

The solubility of the polymers employed in this invention varies considerably in a selected hydrophilic liquid. For example, completely hydrolysed styrene-maleic anhydride copolymer is about 2% soluble in water but at least 20% soluble in a 1:1 mixture of methanol and water. Thus, the desired amount of copolymer can be contacted with the material to be encapsulated by high dilutions in water or, preferably, by the addition of a solubilizing agent, e.g., another hydrophilic liquid. A type of solubilizing agent useful when carboxylic acid polymers are employed are the polysaccharides, e.g., alginates, pectins, methyl cellulose, and carboxymethylcellulose. Of particular usefulness are the galactose polysaccharides, e.g., those derived from Irish moss (carrageen), available as SeaKem Type No. 1 from Seaplant Chemical Corporation, New Bedford, Massachusetts. For example, the solubility of completely hydrolyzed styrene-maleic anhydride copolymer in water can be raised from about 2% to about 7 to 10% in the presence of relatively small amounts of this polysaccharide, e.g., one part to four parts of the copolymer.

Generally speaking, in the process of the invention, any of the recently developed liquid-liquid phase separation techniques for coating almost any type of particle, whether lipophilic or hydrophilic in its surface characteristics can be used. The particles can be liquid or solid in physical structure. The liquid particles can be homogeneous or can contain one or more active ingredients or dispersed emulsion particles. The solid particles can be untreated or can be precoated by phase separation techniques or any other suitable method. It is to be understood that any liquid-liquid phase separation process may be used for forming the membrane.

Suitable coacervation processes which may be used as the liquid-liquid phase separation process are those disclosed in British Patent Specification No. 751,600, which describes encapsulation of microscopic oil droplets which can contain dissolved or suspended materials by simple and complex phase separation.

In the processes described therein phase separation is induced, for example, by the addition of a salt in the case of simple phase separation and by the addition of excess solvent (i.e., water) or adjustment of pH in the case of complex phase separation. Salts which are suitable for inducing simple phase separation include salts having metal, e.g., alkaline earth and alkali-metal, for example potassium and lithium, magnesium, ammonium cations and organic or inorganic anions, e.g., sulphate, phosphate, citrate, acetate, formate, chloride, bromide, nitrate, thiocyanate, and iodide anions. The magnesium cation is ordinarily more efficacious than the lithium cation and the sulphate anion is ordinarily more efficacious than the iodide anion. The anion exerts a more profound influence on the efficacy of the salt than does the cation. Sodium sulphate and ammonium sulphate are highly efficacious for present purposes. The salt should be added in amounts sufficient to produce a significant percentage thereof by weight per volume of the resulting mixture, e.g., 1 to 50% and preferably 3 to 20%.

Similarly, small droplets of hydrophilic liquid-in-oil emulsions can be encapsulated by the process of the invention. The term hydrophilic liquid is intended to refer to water, aqueous solutions or suspensions, and non-aqueous solutions or suspensions immiscible in the oil phase of the emulsions. In preparing encapsulated droplets of this type, an anti-inversion agent, such as hydrogenated castor oil, capable of preventing the inversion of the liquid-in-oil emulsion to an oil-in-hydrophilic liquid emulsion is incorporated in the oil phase of the initial or primary emulsion. Suitable anti-inversion agents include surface active agents, preferably those of the non-ionic type, and oil-thickening agents such as the natural and synthetic waxes, solid fats, sterols, and other conven-

tional oil-gelling or oil-thickening agents. Advantageously, the internal phase of the said emulsions can also, itself, contain a thickening agent, such as methyl cellulose, for increasing its viscosity and thereby reducing the escaping tendency of any active ingredients dissolved or suspended therein. Agents employed for this purpose include the gelable hydrophilic colloids and other viscosity-increasing materials substantially insoluble in the oil phase. The thus prepared emulsion is dispersed in an aqueous sol of a gelable hydrophilic colloid, such as gelatin, at a temperature above the gel point of the said colloid to form a double emulsion. To this is added an aqueous solution of a separation inducing agent, such as sodium sulphate, to bring about phase separation. The intermixture of the emulsion containing colloid solution with the salt solution is preferably carried out over a period of between about one-half to about two hours. Such a process is described and claimed in our copending Application No. 37939/59 (Serial No. 911,483).

Complex phase separations enclosing hydrophilic liquid-in-oil emulsions as above defined wherein the separating phase includes as a component at least one gelable hydrophilic colloid, such as gelatin, and at least one linear macromolecular synthetic polymer as hereinbefore defined such as styrene-maleic acid copolymer may also be used in the process of this invention. In phase separations of this type, a primary hydrophilic liquid-in-oil emulsion containing an anti-inversion agent is prepared as above, and the said primary emulsion is dispersed in an aqueous sol of the aforesaid colloids to form a double emulsion. The pH of the said double emulsion is then adjusted to the separation range of the particular colloids involved, thereby causing a coating to form about the particles of the said secondary emulsion, as above. Such pH adjustment is preferably carried out over a period of between about one-half hour to about two hours. Such a process is described and claimed in our copending Application No. 40224/59 (Serial No. 929,408).

Oil-in-hydrophilic liquid emulsions may also be encapsulated by liquid phase separation in the present invention. Such emulsions are prepared by the techniques of simple and complex phase separation alluded to above, except that the hydrophilic liquid phase must be rendered immiscible with aqueous media which it encounters in the course of phase separation, i.e., aqueous solutions of separation inducing agents and aqueous sols or solutions of the separating colloids, or other materials tending to disturb the integrity of the hydrophilic liquid phase of the initial emulsion. Such integrity is obtained by the addition of certain thickening agents, such as methyl cellulose, to the hydrophilic liquid phase. Phase separation is induced essentially as above over the period of time indicated. Such processes are described and claimed in our copending Applications Nos. 37941/59 and 40227/59 (Serial Nos. 929,402 and 929,409).

Membranes produced by the procedures as generally outlined above but in which phase separation is induced by dilution with a non-solvent in which the colloid is less soluble than it is in water are also improved by the hardening process of the present invention.

The process of the invention may also be used to encapsulate solid particulate matter to which, if not already lipophilic in character, a solid lipophilic coating, such as beeswax, has been applied prior to coating. This may itself be applied by liquid-liquid phase separation from the aqueous systems described above.

As used herein, by the term "lipophilic" we mean a surface having a stronger attraction for low dielectric constant, non-polar media than for high dielectric constant, polar media.

After the separating phase has collected around the dispersed particles in a liquid form, it can be gelled or otherwise set by conventional techniques as desired. For example, gelling can be brought about by lowering the temperature below the gel point of any gelable component of the coacervate. Similarly, the synthetic polymers can be set by pH adjustment.

Subsequent to treatment of the membrane as desired, the encapsulated particles can be most advantageously irradiated, after separation from the equilibrium liquid existing after the by conventional means, illustratively filtration or centrifugation, as a suspension in water. After irradiation, the hardened capsules are separated by conventional means and dried by any suitable technique, e.g., spray drying, freeze drying or air drying.

Irradiation of the coated material by the present process preferably involves the use of high speed electrons such as beta rays or cathode rays. However, gamma rays (i.e., electromagnetic waves of very short wave lengths produced by disintegrating atoms of radioactive elements) and X-rays (i.e., electromagnetic waves very similar to gamma rays but generally having somewhat longer wave lengths produced by the impact of rapidly moving electrically charged particles on a metal target in a vacuum tube) are also useful. When the encapsulated particles are subjected to irradiation as indicated, it is not known exactly what changes take place; but it is known that the reaction is irreversible and results in a membrane which is harder and more impermeable. Such irradiation also produces a sterile product.

In order to be suitable for present pur-

poses, the radiation used must have enough energy to ionize and penetrate the mass of the material being irradiated. The use of a Van de Graaff electron accelerator as a source for high speed electrons is preferred in the process of the present invention. However, any source of high energy electrons, such as electron accelerators, linear accelerators, and radioactive substances, are also suitable. One million electron volts (1 mev) produced by the Van de Graaff electron accelerator has sufficient energy to penetrate 5 mm. of water or an equivalent mass; 2 mev has sufficient energy to penetrate 1 cm. of water or an equivalent mass. The encapsulated particles have been successfully irradiated with an electron beam from a Van de Graaff electron accelerator at radiation dosages from 0.125×10^6 to 16.000×10^6 rep. In one embodiment of the present invention, the encapsulated particles are suspended in sufficient water to make a thick slurry, and the suspension spread evenly in shallow containers. The depth of the water suspension is adjusted to a level consistent with the energy of the beta rays to be used. The suspension is then subjected to irradiation at dosages sufficient to bring about the desired degree of hardening.

Examples of radioactive substances which can be used in the present process include strontium-90 which ultimately yields beta rays rated at 2.18 mev and cobalt-60 which emits gamma rays. The type of X-ray machine used as a source of radiation is not particularly critical, the machine used being selected or designed to meet the physical or manipulative requirements of the product being irradiated.

Combinations of the various forms of radiation indicated above can also be used.

The following examples are illustrative of the process and product improvement of the present invention but are not to be construed as limiting.

EXAMPLE 1

A suspension of 8 gm. of methylcellulose and 50 gm. of caffeine in 100 ml. of water is heated to 80° C. One hundred milliliters of mineral oil is heated to 80° C. and emulsified into the aqueous suspension. Seventy-five grams of styrene-maleic acid copolymer is dispersed in 1500 ml. of water, heated to 80° C., and sufficient 10% sodium hydroxide is added to dissolve the copolymer. The emulsion is then dispersed in the copolymer sol with agitation. Seventy-five grams of gelatin is dispersed in 500 ml. of water, heated to 80° C., and 10% sodium hydroxide is added to raise the pH to 7. The gelatin sol is then added dropwise to the emulsion-copolymer mixture with continuous stirring. Immediately thereafter is added dropwise over the period of one hour a sufficient amount of 20% acetic acid solution to bring the pH of the mixture down to 3.9. The material is maintained at 80° C. for 15 min., then cooled to 4° C. over a period of 30 min. The encapsulated material is then separated by centrifugation and resuspended in 300 ml. of water. The suspension is then spread into "Pyrex" trays in 1 mm. layers and subjected to 2 mev irradiation from the Van de Graaff electron accelerator until a dose of 2.000×10^6 rep is reached. ("Pyrex" is a Registered Trade Mark.) The hardened capsules are then separated by filtration and freeze dried to produce a sustained action oral stimulant.

Other thickening agents can be substituted for the methyl cellulose above in equal amounts, such as, for example, acacia, tragacanth, carboxymethylcellulose, magnesium aluminum silicate, the polyglycols, glycerin, and syrups.

Similarly, other hydrophilic colloids such as agar-agar, albumin, fibrinogen, and other synthetic polymers such as styrene-maleic acid amide, the sulphonated polystyrenes, starch acetate phthalate, cellulose acetate phthalate, amylose acetate phthalate, polymethacrylic acid, and methylvinyl ether-maleic acid can be substituted for the styrene-maleic acid above.

EXAMPLE 2

A water-in-oil emulsion is prepared at 40° C. by emulsifying into 37 gm. of lanolin containing 0.25 gm. of polyoxyethylene sorbitan monostearate 30 ml. of water in which is dissolved 0.01 gm. of sulphanilamide. A sol comprising 15 gm. of fibrinogen in 150 ml. of water is heated to 40° C. and thoroughly mixed with the said emulsion. To the resulting mixture is introduced slowly 150 ml. of a 20% solution of sodium sulphate over a period of one and one-half hours with vigorous stirring. The temperature of the resulting equilibrium liquid containing the phase coated emulsion is reduced to 7° C. to gel the fibrinogen. The resulting encapsulated particles are then separated from the equilibrium liquid by filtration and resuspended in 100 ml. of water. The suspension is then spread into shallow trays of heat resistant glass in 1 mm. layers and subjected to 1 mev radiation from a Van de Graaff generator until a dose of 0.125×10^6 rep is reached. The hardened product is separated by centrifugation, resuspended in water and spray dried. The encapsulated particles thus prepared can be incorporated in an ointment in the usual manner for topical use.

EXAMPLE 3

Ten grams of glyceryl monostearate is melted by heating to 60° C., and 20 gm. of mercuric oxide is dispersed therein. A solution of 6 gm. of acacia in 48 ml. of water is prepared and heated to 60° C. The re-

sulting solution is adjusted to pH 3.9 by the addition of 20% acetic acid solution. A gelatin sol is prepared by dispersing 6 gm. of gelatin in 48 m. of water. The resulting sol is adjusted to pH 3.9 by addition of 20% acetic acid solution. Each of the above three fractions is heated to 60° C. With vigorous stirring, the mercuric oxide-glyceryl monostearate mixture is dispersed in the acacia solution, and with continued stirring, the gelatin sol is slowly added thereto. Approximately 90 ml. of water also heated to 60° C. is added dropwise to the resulting mixture over the period of 30 minutes to produce a phase coating about the particles of glyceryl monostearate which in turn envelopes the particles of mercuric oxide. When addition of the 90 ml. quantity of water is complete, the temperature is maintained at 60° C. for an additional 15 minutes followed by rapid cooling to 5° C. by the addition of 70 gm. of ice and 500 ml. of water at 0° C. The resulting mixture is maintained below 5° C. for two and one-half hours. The coated mercuric oxide particles are separated by centrifugation and redispersed in 75 ml. of water. The suspension is then spread into "Pyrex" trays in approximately 1 mm. layers and subjected to 1.5 mev radiation from a Van de Graaff electron accelerator until a dose of 4.000×10^6 rep is reached. The encapsulated material is then separated by centrifugation and freeze dried to produce a useful veterinary anthelmintic.

EXAMPLE 4

Chloral hydrate - - -	100 gm.
Mineral oil - - - - -	125 ml.
Beeswax - - - - -	25 gm.
Styrene-maleic acid copolymer	75 gm.
Gelatin - - - - - -	75 gm.

Dissolve 100 gm. of chloral hydrate in 50 ml. of water and heat to 70° C. Dissolve 25 gm. of beeswax in 125 ml. of mineral oil at 70° C. Emulsify the aqueous solution into the oil solution by passing the combined mixture through a hand homogenizer 4 times. Disperse 75 gm. of styrene-maleic acid copolymer in 1500 ml. of water, heat to 70° C. and add sufficient 10% sodium hydroxide to dissolve the copolymer. (At this point the copolymer solution has a pH between 7 and 8.) With continuous agitation, disperse the emulsion in the copolymer sol. Dissolve 75 gm. of gelatin in 500 ml. of water at 70° C. and add 10% sodium hydroxide to raise the pH of the sol to 7. Add the gelatin sol dropwise to the copolymer-emulsion mixture with continuous stirring. Immediately thereafter, with the temperature at 70° C. and with continuous stirring, add dropwise over the period of two hours 20% acetic acid solution to bring the pH of the mixture down to 4.5. Maintain the mixture at 70° C. with stirring for 30 minutes, and then cool to 6° C. over a period of 30 minutes. Maintain the material below 10° C. for 1 hour. The encapsulated particles are separated by filtration and resuspended in 500 ml. of water. The suspension is then spread into "Pyrex" trays in approximately 1 mm. layers and subjected to 2 mev irradiation from a Van de Graaff electron accelerator until a dose of 1.000×10^6 rep is given. The encapsulated particles are filtered and air dried to produce a sustained action sedative.

EXAMPLE 5

Crystal violet lactone having the formula 3,3 - bis(p - dimethylaminophenyl)6 - dimethylamino phthalide is dissolved to the extent of 3% by weight in trichlorodiphenyl. One gallon of an oil-in-water emulsion containing 20 parts by weight of the trichlorodiphenyl and 100 parts by weight of a sol of 10% by weight of pigskin gelatin having an isoelectric point of pH 8 in water is prepared. Emulsification is continued until the drop size of the oil is from 2 to 5 microns. This material is kept at 50° C. to prevent gelation of the gelatin. With the temperature kept at 50° C., phase separation is induced by adding slowly and uniformly, four-tenths of a gallon of sodium sulphate in water over a period of one hour with continuous agitation. The gelatin molecules are thus deposited uniformly about each oil droplet as a nucleus. The heated mixture is then poured into 10 gallons of 7% by weight of sodium sulphate in water at 4° C. with agitation to gel the gelatin. The material is filtered and washed with water while the temperature is kept below the gel point of the gelatin to remove the salt. The filtered material is then exposed to 2.000×10^6 rep of gamma radiation from a cobalt-60 source. The irradiated encapsulated particles are ready for application to a sheet of paper which is then dried to form a transfer film. When marking pressures break the capsules and release the oil, it contacts a sensitized undersheet containing attapulgite and transfers the markings to the undersheet as desired.

EXAMPLE 6

A sol is made of 20 grams of gum acacia dissolved in 160 grams of water. Into this is emulsified 80 grams of trichlorodiphenyl. A second sol of 20 grams of pork skin gelatin, having its isoelectric point at pH 8, and 160 grams of water is prepared, and this second sol is mixed with the emulsion. A volume of water is added to the mixture by spray over the period of one hour with constant stirring. All of the foregoing steps are carried out with the ingredients at 50° C. The resulting mixture is poured into water at 0° C., enough water being used to bring the total weight of ingredients to

3960 gm. The mixture is agitated and thereafter is allowed to stand for an hour at not over 25° C. The formation of the capsules is now completed, and they can be separated by centrifugation and placed into a heat resistant glass container. The material is then subjected to 0.125×10^6 rep of X-ray irradiation by the use of a Van de Graaff generator in which the electron window has been removed and a water cooled metal plate, serving as a target for X-ray propagation, substituted therefor. If it is desired to use the capsules as a coating material for paper, the encapsulated particles can be applied to the paper.

EXAMPLE 7

A mixture of 12 grams of styrene-maleic acid copolymer, 3 grams of SeaKem, Type No. 1, and 12 grams of gelatin was dispersed in a liquid consisting of 218 milliliters of 0.5 N dibasic sodium phosphate and 240 milliliters of water. The mixture was heated to 80° C. and stirred until the solids had dissolved. Then 105 milliliters of white mineral oil was heated to 80° C. and emulsified into the aqueous sol utilizing a homogenizer. With constant stirring of the emulsion, a mixture of 65.5 milliliters of 1.0 N citric acid and 75 milliliters of water, previously heated to 80° C., was added dropwise to the emulsion. The material was then cooled to room temperature to gel the coacervate. The encapsulated product was separated by centrifugation and resuspended in 100 milliliters of water. This suspension was used directly in the irradiation studies.

Aliquots of 5 grams of the coacervate suspension were placed in 10-cm. Petri dishes and subjected to irradiation in the Van de Graaff electron accelerator.

The irradiated samples were tested to determine the effect of the irradiation on the membrane. If the membrane had been hardened this would be evidenced by a more persistent retention of the oil when the material was subjected to heating and centrifugation.

The encapsulated material contained a sufficiently high percentage of encapsulated oil to "surface" the product when suspended in water and subjected to centrifugation. A coacervate membrane from which the oil had been released would precipitate under the same conditions. Therefore, when a given sample of encapsulated material is suspended in water and subsequently subjected to centrifugation, the amount of precipitate formed is an indication of the amount of oil which has been released from the product.

The precipitation test was applied to the irradiated materials. A one gram sample was suspended in 20 milliliters of 0.5 N Na_2HPO_4 and heated by this treatment.

The mixture was placed in a 40-milliliter conical centrifuge tube and centrifuged for 15 minutes in 1500 rpm. After centrifugation the height of the precipitate was measured. The results are given in the following table:—

Dose of irradiation in Van de Graaff electron accelerator	Height of liquid in centrifuge tube	Thickness (height) of precipitate
0	76 mm.	45 mm.
0.125×10^6 rep	70 mm.	3 mm.
0.250×10^6 rep	69 mm.	3 mm.
0.500×10^6 rep	69 mm.	2 mm.
1.000×10^6 rep	69 mm.	2 mm.
2.000×10^6 rep	70 mm.	2 mm.
4.000×10^6 rep	69 mm.	1 mm.
8.000×10^6 rep	69 mm.	1 mm.
16.000×10^6 rep	69 mm.	1 mm.

The results clearly show that the non-irradiated sample produced a significantly greater amount of precipitate than did the irradiated samples. This is interpreted as an increased ability of the irradiated samples to retain oil. The data also show a trend indicating that a higher dose of radiation increases this ability.

WHAT WE CLAIM IS:—

1. A process for the production of particles of material each encapsulated by a membrane comprising polymeric material, which includes the steps of: (1) forming the membranes about the particles of material by a liquid-liquid phase separation process; (2) setting the membranes; (3) hardening the membranes by irradiation thereof with beta rays, gamma rays, or X-rays.

2. A process according to Claim 1 in which the membrane contains a gelable hydrophilic colloid.

3. A process according to Claim 2 in which the gelable hydrophilic colloid is gelatin or gum acacia.

4. A process according to any preceding claim in which the membrane contains a linear macromolecular synthetic polymer as hereinbefore defined.

5. A process according to Claim 4 in which the linear macromolecular synthetic polymer is a styrene-maleic acid copolymer.

6. A process according to any preceding

claim in which the particles of material are particles of solid material having an essentially lipophilic surface.

7. A process according to any preceding claim in which the particles of material are particles of oil or particles composed of an oil-in-hydrophilic liquid emulsion, in which the hydrophilic liquid contains a thickening agent, or particles composed of a hydrophilic liquid-in-oil emulsion, in which the oil contains an anti-inversion agent.

8. A process according to any preceding claim in which the particles of material have dissolved or suspended therein one or more active ingredients as hereinbefore defined.

9. A process according to any preceding claim in which the membranes are set while in a liquid medium and the encapsulated particles are then separated from the liquid medium and are suspended in water before being irradiated.

10. A process for the production of encapsulated particles substantially as herein described with reference to any of the examples.

11. Encapsulated particles whenever produced by a process as claimed in any preceding claim.

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